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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/787,810	03/21/2001	Richard Anthony Flynn	51301-00003	8199

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EXAMINER	
HAWES, PILI ASABI	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 04/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/787,810	FLYNN ET AL.	
	Examiner	Art Unit	
	Pili A. Hawes	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21,23-25 and 29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21,23-25,29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The examiner acknowledges receipt of Applicant's Remark/Arguments filed 2/6/2004.

Specification

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-21, 23-25, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Clark et al. (US 5641510), and further in view of Rose et al. ("Evaluation of Sodium Colistimethate Aerosol") and Catchpole et al. ("A reassessment of the in-vitro activity of colistin sulphomethate sodium").

Clark discloses capsules (such as hard gelatin, cellulose and plastic capsules) containing pharmaceutical powders which are administered to a patient via inhalation are treated so as to increase the effective amount of the pharmaceutical agent reaching the respiratory system of the patient. The capsules are coated internally with a lubricant during manufacture. The lubricant-coated capsule is dusted internally with a dusting agent such as a salt (e.g. sodium chloride) or a sugar (e.g. lactose, mannitol, trehalose or sucrose) prior to inserting the pharmaceutical powder inside the capsule (see abstract). This method serves to improve aerosol delivery of the pharmaceutical powder to the patient. The term "pharmaceutical powder" refers to a powder containing at least a pharmaceutical compound and, optionally, a pharmaceutical acceptable carrier or

excipient. The pharmaceutical powder is generally administered to the respiratory tract of the patient in the form of an aerosol. Examples of pharmaceutical compounds which might usefully be incorporated into the hard gelatin capsule include pharmaceutical polypeptides, antibacterials and antibiotics (see cols. 5 and 6). A mixture of pharmaceutical compound particles and an excipient can form the pharmaceutical powder. Examples of pharmaceutically acceptable carriers or excipients include, but are not limited to, salt compounds (e.g. sodium chloride) or sugar compounds (e.g. glucose, fructose, lactose, mannitol, trehalose and sucrose). Other conventional agents such as those which are conventionally incorporated into dry powder inhalant compositions may be present in the pharmaceutical powder. The average particle size of the particles of the pharmaceutical powder containing the therapeutic agent is preferably in the range 0.1 to 20 micrometers, more preferably 1 to 6 micrometers. Typically, at least 50% of the particles will be of a size, which falls within this range, although the presence of significant quantities of fine materials is contemplated within the scope of the invention (see col. 5 lines 1-13). The pharmaceutical powder having the desired average particle size can be prepared by dry mixing the pharmaceutical compound and the excipient. Clark does not teach the antibiotic to be colistin sulphomethate sodium.

Rose discloses the evaluation of sodium colistimethate aerosol in gram-negative infections of the respiratory tract. Sodium colistimethate (SCM), the methane sulfonate derivative of colistin, is bacterial and active against many strains of gram-negative bacilli. SCM is used for aerosol therapy, dissolved in sterile water and administered by intermittent positive pressure breathing instruments yielding a particle size of 1-7

microns. SCM in aerosol form is well tolerated by all patients except one, who in addition to obstructive pulmonary disease, suffered from angina pectoris. Daily dosages ranging from 75 to 300 mg, given one to three times a day, given one to three times a day, resulted in pathogen free sputum cultures in 60% of the patients. The results of the study indicate the aerosolized SCM is well tolerated and effective in eradicating or suppressing susceptible gram-negative organisms carried in the respiratory tract of patients with underlying pulmonary disease.

Catchpole discloses a reassessment of in-vitro activity of colistin sulphomethate sodium. Colistin is known to be used as inhaled therapy for treatment of infection by *Pseudomonas aeruginosa* in patients with cystic fibrosis. The in-vitro activity of colistin sulphomethate sodium was compared with that of other commonly used antibiotic agents against 377 recent clinical isolated of Gram-negative bacterial, including 94 strains of *Pseudomonas aeruginosa* from patients with cystic fibrosis. The results show that colistin remains a useful antimicrobial agent against Gram-negative bacteria, particularly those strains that are resistant to more commonly used antibiotics (see abstract).

Absent unexpected results, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the composition of Clark by substituting colistin sulphomethate sodium as taught by Rose and Catchpole for the antibiotic taught by Clark because of the expectation of producing a composition that is "well tolerated and effective in eradicating or suppressing susceptible gram-negative organisms carried in the respiratory tract of patients with underlying pulmonary disease"

as taught by Rose and provide an added advantage of " a useful antimicrobial agent against Gram-negative bacteria, particularly those strains which are resistant to more commonly used antibiotics" as taught by Catchpole. Colistin sulphomethate sodium is known to be in micronized particles as taught by Rose. Therefore, the expected result would be micronized particles, with the desired diameter mixed with a carrier in the desired ratio of colistin sulphomethate sodium to carrier.

Response to Arguments

Applicant's arguments filed 02-06-2004 have been fully considered but they are not persuasive.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Applicants argue that Catchpole teaches colistin sulphomethate sodium is effective when dissolved in solution, and not as a dry powder. This argument is not persuasive. Applicants themselves admit colistin sulphomethate sodium has long been known to be effective treatment, particularly in the form of inhalation, for infections caused by Gram-negative organisms. Catchpole showed that colistin remains a useful

anti-microbial agent. Catchpole does not specifically teach that colistin sulphomethate sodium is not effective in its powder form, or **only** effective if administered as a solution.

Applicants also argue that Dodd discloses the inhalation of overly strong solutions of colistin have negative effects on the patients and result in discontinued treatment. Additionally, applicant argues Rose teaches a solution form of colistin derivative, sodium colistimethate, nebulized to form an aerosol for inhalation, used to treat patients with Gram-negative bacterial infections. Rose teaches that no toxic symptoms were manifested in any of the patients (page 277) receiving treatment.

The solutions of colistin taught by Catchpole, Dodd, and Rose are not at issue. Each reference teaches the use of colistin derivatives in treating bacterial infections by inhalation. The teachings of negative side effects of hypertonic colistin solutions disclosed by Dodd would motivate one skilled in the art to prepare other embodiments of colistin or its derivatives to take advantage of its antibacterial properties as taught by Catchpole, the benefits of administering colistin or its derivatives by aerosol inhalation as taught by Rose, and would seek to minimize its negative side effects when administered in solution. Clark discloses such an embodiment, Clark teaches the efficacy of administrating pharmaceutically active powders via inhalation. Therefore it is the position of the examiner that one skilled in the art would have been motivated to use a powder form of colistin sulphomethate sodium with reasonable expectation of success.

Applicants argue they surprisingly found that micronized particles of colistin sulphomethate sodium powder do not clump or stick as one would expect. Clark

teaches the use of a "pharmaceutically acceptable dusting agent" (col. 6) used to prevent adherence of the pharmaceutically active powder to the capsule. It also teaches that the use of such a dusting agent can result in enhanced delivery of the drug from the capsule (col. 12). Clark discloses a method of preventing adherence of the powder to capsule walls and of obtaining a more consistent delivery of the dry powder via inhalation. It is the position of the examiner that particles are sticking or clumping together when they are adhering to the capsule walls. Therefore it is the position of the examiner that the results found by Applicants are not surprising in view of Clark's teachings.

Applicants argue Clark's invention is particularly relevant for low dosage therapeutic proteins. The examiner has considered Applicants arguments and does not find them persuasive. Clark discloses in addition to pharmaceutical polypeptides, the use of other pharmaceutically active compounds "which might usefully be incorporated into hard gelatin capsules". As the Applicants point out, Clark lists antibacterials (col. 6) among the list of pharmaceutically active compounds. Clark teaches the embodiment of inhalation therapy using dry pharmaceutical powder. Rose and Catchpole teach the specific colistin derivatives and their effectiveness against bacterial infections.

Therefore it is the position of the examiner it would have been obvious to one of ordinary skill in the art at the time the inventions was made to substitute sodium colistimethate taught by Rose and Catchpole for the pharmaceutical powder taught by Clark with the expectation of obtaining or producing a composition that is "well tolerated and effective in eradicating or suppressing susceptible Gram-negative organisms

carried in the respiratory tract of patients with underlying pulmonary disease" taught by Rose and provide an added advantage of "useful antimicrobial agent against Gram-negative bacteria, particularly those strains which are resistant to more commonly used antibiotics" as taught by Catchpole.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Pili A. Hawes whose telephone number is 571-272-8512. The examiner can normally be reached on 8-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page can be reached on 571-272-0602. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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AU-1615

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